



Use of Mathematical Optimization Models to Derive Healthy and Safe Fish Intake

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Published in:
Journal of Nutrition

Link to article, DOI:
[10.1093/jn/nxx010](https://doi.org/10.1093/jn/nxx010)

Publication date:
2018

Document Version
Peer reviewed version

[Link back to DTU Orbit](#)

Citation (APA):
Persson, M., Fagt, S., Pires, S. M., Poulsen, M., Vieux, F., & Nauta, M. (2018). Use of Mathematical Optimization Models to Derive Healthy and Safe Fish Intake. *Journal of Nutrition*, 148(2), 275-284. <https://doi.org/10.1093/jn/nxx010>

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Title: Use of mathematical optimization models to derive healthy and safe fish intake ^{1, 2, 3, 4}

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Word count (introduction through discussion): 4,850

Number of figures: 7

Number of tables: 4

Online Supporting Material submitted

Running title: Optimization of individual fish intake

¹ The preparation of this manuscript was funded through the Metrix project by the Ministry for Environment and Food in Denmark.

¹ Author disclosures: M. Persson, S. Fagt, S. M. Pires, M. Poulsen, F. Vieux, M. J. Nauta, no conflicts of interest.

³ Supplemental Tables 1–4 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at <http://jn.nutrition.org>.

⁴ Abbreviations used: DANSDA, Danish national survey of diet and physical activity; DHA, docosahexaenoic acid; dl-PCBs, dioxin-like polychlorinated biphenyls; EPA, eicosapentaenoic acid; LB, lower bound; LOD, limit of detection; LOQ, limit of quantification; QP, quadratic programming model allowing all species of fish in modeled intake; QPr, quadratic programming model only allowing reported fish in modeled intake; UB, upper bound; 2D, two-dimensional; 8D, eight-dimensional.

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1 **Abstract**

2 **Background.** Recommended fish intake differs substantially from observed fish intake. In Denmark,
3 around 15% of the population meets the Danish recommendation on fish intake. How much fish
4 individuals eat varies greatly. There are so many different patterns of fish intake that the fish intake of
5 the average population cannot reflect this.

6 **Objective.** We developed a method that may provide realistic and achievable personalized dietary
7 recommendations based on an individual's body weight and current fish intake. The objective of the
8 study was to propose specific fish intake levels for individuals that meet the recommendations for
9 eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and vitamin D without violating the
10 tolerable intake recommendations for methyl mercury, dioxins, and polychlorinated biphenyls (dl-
11 PCBs).

12 **Methods.** Two mathematical optimization models were developed that apply quadratic programming
13 to model personalized recommended fish intake, fulfilling criteria on nutrients and contaminants, while
14 simultaneously deviating as little as possible from observed individual intake. A recommended intake
15 for eight fish species was generated for each individual in a group of 3,016 Danes (1,552 women and
16 1,464 men, ages 18-75), whose fish intakes and body weights were known from a national dietary
17 survey.

18 **Results.** Individual, personal dietary recommendations were successfully modeled. Modeled fish
19 intake levels were compared with observed fish intakes. For women, the average proposed increase
20 in fish intake was 14 g/wk for lean fish and 63 g/wk for fatty fish; and for men these numbers were 12
21 g/wk and 55 g/wk, respectively.

22 **Conclusions.** Using fish intake as an example, we show how quadratic programming models may be
23 used to advise individual consumers on the optimization of their diet, taking both benefits and risks

into account. This approach has the potential to increase compliance with dietary guidelines by targeting the individual consumers and minimizing the need for large and eventually unrealistic behavior changes.

Key words: dietary habits, diet optimization model, quadratic programming, risk-benefit assessment, Denmark, adults, nutrients, contaminants

Introduction

The research area *risk-benefit assessment of foods* focuses on comparing food-related health risks and benefits (1–3). Today, about 70 % of all risk-benefit assessments of foods have analyzed fish (1,4–8). Fish is associated with health benefits, mainly due to its content of essential long-chain fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), but also vitamins and minerals. However, being the one significant source of methyl mercury, and containing organic pollutants, the health risks from fish consumption need to be critically considered. According to a risk-benefit assessment of fish in the Norwegian diet (6), positive health effects from fish consumption are especially due to its content of the nutrients EPA, DHA, and vitamin D, whereas methyl mercury, dioxins, and dioxin-like polychlorinated biphenyls (dl-PCBs) are contaminants in fish, posing a relevant risk to human health. These nutrients and contaminants are representing the benefits and risks included in this study, based on the assumption that the Danish diet is comparable to the Norwegian diet. Hence, a fish intake that meets constraints on these nutrients is defined as healthy, and similarly, a fish intake that meets constraints on these contaminants is defined as safe.

Risk-benefit assessments have shown that health benefits of fish consumption outweigh the potential risks in a population (4,6). Based on this, the recommended intake of fish in the Danish official dietary guidelines is 350 g/wk of which 200 g should be fatty fish (9). However, most Danes do not meet these guidelines. According to the Danish National Survey of Diet and Physical Activity (DANSDA)

(10), the observed average fish intake in Denmark ($n = 3,016$, ages 18-75) was 222 g/wk of which 120 g was fatty fish. Species with fat content higher than 5% are classified as fatty fish (6). The standard deviation of total fish intake was 228 g/wk. This large variation is partly due to 329 individuals (11%) in the study population who did not report consumption of fish during one week. Furthermore, only 445 (15%) of the individuals met the Danish official dietary guideline recommendation on fish.

Mathematical optimization has previously been used to analyze if and how diets could be changed to fulfill several health-related criteria, both on population level (11,12) and for individuals (13,14). Many of the previous diet optimization studies have constructed food intake meeting several criteria, while simultaneously deviating as little as possible from the observed intake. The arguments were that new intakes that differ least from current intakes were the most realistic and achievable for consumers.

Previous fish intake optimizations and risk-benefit assessments of fish have studied average population fish intake (5,6) and random fish intake scenarios (4). In this study, self-reported fish intakes for 3,016 individuals were considered, and thereby, a personalized recommended fish intake was obtained for each individual in the study population. Since personal recommendations were of interest, the intake for each individual in the study population was optimized separately and no inference to the rest of the population was made. Quadratic programming techniques were used as compared with linear programming that has been used in several previous diet optimization studies (5,11–14).

We developed a method that may provide realistic and achievable personalized dietary recommendations based on an individual's body weight and current reported intake. The objective of the study was to propose specific fish intake levels for individuals that meet the recommendations for EPA, DHA, and vitamin D without violating the tolerable intake recommendations for methyl mercury, dioxins, and dl-PCBs. By minimizing the need for large and eventually unrealistic behavior changes, a new intake was generated for each individual in the study population, that is the selected DANSDA

71 study participants (n=3,016, ages 18-75). Since fish may not be the only source of the nutrients and
72 contaminants considered, different background exposure scenarios were compared.

73 **Methods**

74 A mathematical optimization model minimizes (or maximizes) an objective function subject to
75 constraints. The optimization variable that minimizes (or maximizes) the objective function with respect
76 to the given constraints is the solution to the problem. A quadratic programming problem has a
77 quadratic objective function and linear constraints, and is a special case of the general convex
78 optimization problem: optimization of a convex function over a convex set. This convexity property
79 guarantees that a minimum (or maximum) found is a global minimum (or maximum) (15). Furthermore,
80 the objective function of a quadratic problem is strictly convex, which guarantees that a minimum
81 found is a unique global minimum.

82 Two mathematical quadratic programming models were developed: QP and QPr, which differ by one
83 constraint only. The optimization variable of the models denotes weekly intake amounts of different
84 types of fish for one individual. The objective function minimizes the sum of the square of the
85 deviations between the observed intake (from individual intake data) and the optimized (by the model)
86 intake. The constraints ensure that the optimized intake meet weekly lower limits on the nutrients EPA
87 + DHA and vitamin D, without violating weekly upper limits on the contaminants methyl mercury and
88 dioxins + dl-PCBs (See 2.3). The QP model allows non-reported fish to be added in the modeled
89 intake, whereas the QPr model only allows reported fish in the modeled intake. For each individual, a
90 non-reported fish is a species of which she/he reported a zero intake. Hence, for an individual who
91 does not consume fish, all species of fish are non-reported. The QP model was considered most
92 relevant because the observed intakes were 7-day estimated records and other species of fish may
93 well have been consumed by an individual during another week.

The models were run both as two-dimensional and eight-dimensional (2D and 8D). The 2D models optimize the sub-groups lean and fatty fish, whereas the 8D models optimize the four most consumed fish species per sub-group. The intakes of the study population, obtained from DANSDA, are reported on specie-level. Species with fat content higher than 5% are classified as fatty fish (6). For the 2D models, the reported intake of one individual is translated to amounts of lean and fatty fish by this classification.

Quadratic programming models

The QP models are expressed as

$$\underset{\mathbf{x}}{\text{minimize}} \quad f(\mathbf{x}, \mathbf{x}_{\text{obs}})$$

$$\text{subject to} \quad \mathbf{B}\mathbf{x} \geq \mathbf{b} \quad (\text{a})$$

$$\mathbf{R}\mathbf{x} \leq \mathbf{r} \quad (\text{b})$$

$$\mathbf{x} \geq \mathbf{0} \quad (\text{c})$$

where the vector \mathbf{x} ($d \times 1$) is the optimization variable representing weekly intake amounts of d different fish species or subgroups of fish species; the vector \mathbf{x}_{obs} ($d \times 1$) is a constant vector describing the corresponding observed intake amounts of an individual; and equations (a), (b) and (c) are the constraints of the problem. Besides (possible) additional equality constraints in (c), QPr is identical to QP. The function $f(\mathbf{x}, \mathbf{x}_{\text{obs}})$ is the objective function of the problem. The variable d determines the dimension of the problem. In this study, the models were run with both $d=2$ and $d=8$. For $d=2$, the two elements of the vector \mathbf{x} denote the subgroups lean and fatty fish. For $d=8$, the eight elements of the vector denote the eight species of fish included in the study: cod, plaice, tuna, 'other lean'; and salmon, herring, mackerel and 'other fatty'.

111 **Linear constraints.** The vector \mathbf{b} ($m \times 1$) in constraint (a) defines the weekly lower limits for m different
 112 nutrient intake amounts contributed by fish. These are weekly recommendations for the nutrients
 113 scaled for background exposure, as fish probably are not the only source of the nutrients. In this study,
 114 $m = 2$ (EPA + DHA and vitamin D). The vector \mathbf{r} ($k \times 1$) in constraint (b) defines the weekly upper limits
 115 for k different contaminant intake amounts from fish. These are tolerable weekly intakes of the
 116 contaminants, also scaled for background exposure. In this study, $k = 2$ (methyl mercury and dioxins +
 117 dl PCBs), and each individual gets a specific \mathbf{r} vector, defined by her/his body weight. The matrix \mathbf{B}
 118 ($m \times d$) in constraint (a) describes the mean concentrations of m nutrients for the n different (subgroups
 119 of) fish species. Similarly, the matrix \mathbf{R} ($k \times d$) in constraint (b) describes the mean concentrations of k
 120 contaminants. Consequently, the matrix product $\mathbf{B}\mathbf{x}$ ($m \times 1$) represents the weekly intake amounts of
 121 nutrients from fish and the matrix product $\mathbf{R}\mathbf{x}$ ($k \times 1$) represents the weekly intake amounts of
 122 contaminants from fish. The constraint (c) ensures that no negative intakes occur. For the QPr model,
 123 elements of constraint (c) corresponding to non-reported (subgroups of) fish species are set equal to
 124 zero, instead of greater than or equal to zero. All feasible vectors \mathbf{x} (i.e., vectors that satisfy the
 125 constraints) make up the feasible region of the problem. Among the feasible vectors, the vector that
 126 optimizes the objective functions is the solution to the problem.

127 **Quadratic objective function.** The objective function is defined as the L_2 -norm of $\mathbf{x} - \mathbf{x}_{\text{obs}}$ (the
 128 Euclidean distance between \mathbf{x} and \mathbf{x}_{obs}).

$$f(\mathbf{x}, \mathbf{x}_{\text{obs}}) = \|\mathbf{x} - \mathbf{x}_{\text{obs}}\|_2 = \sqrt{|x_1 - x_{\text{obs},1}|^2 + |x_2 - x_{\text{obs},2}|^2 + \cdots + |x_n - x_{\text{obs},d}|^2}$$

129 The objective function is minimized. Minimizing \sqrt{x} gives the same optimal solution as minimizing \mathbf{x} ,
 130 and when x is real-valued $|x|^2 = x^2$. Hence, for this problem, the objective function can be rewritten to a
 131 quadratic function:

$$f(\mathbf{x}, \mathbf{x}_{\text{obs}}) = (x_1 - x_{\text{obs},1})^2 + (x_2 - x_{\text{obs},2})^2 + \cdots + (x_n - x_{\text{obs},d})^2$$

Each individual gets a specific objective function, defined by her/his observed intake amounts $x_{\text{obs},1}$, $x_{\text{obs},2}$, ..., $x_{\text{obs},d}$. Observe that the objective function is strictly convex and minimized over a convex set, hence a unique global minimum exists.

Observed intake data

Current fish intakes on species-level (7-day estimated records) and self-reported body weights were obtained from DANSDA (10). Individuals younger than 18 years of age were excluded, which resulted in a dataset of 3,016 individuals (1,552 women and 1,464 men) of age 18-75. There were 47 missing values in body weight among the 3,016 individuals in the study population. For those 47 individuals (16 men and 31 women) the gender-specific mean for body weight was used: 69.7 kg for women and 84.4 kg for men. Mean daily intakes were converted to mean weekly intakes by multiplying the mean daily intake by seven.

For each subgroup (lean and fatty fish), the three most consumed species were selected and the remaining species were classified as 'other'. As eel is considered critically endangered, marketing and consumption of European eel is debated, and therefore it was excluded from this study. The individual observed weekly fish intakes along with the recommendation in the Danish official dietary guidelines are shown in **Figure 1**, and the statistics of the intakes are shown in **Table 1**.

Constraint data

Concentrations. Nutrient concentration data were obtained from the Danish food composition database (16). Mean nutrient concentrations were available for different species or subcategories of fish species. Contaminant concentration data were obtained from the EFSA Circle of Trust initiative (17). For mercury, concentrations for several samples per fish species, along with limit of detection (LOD) and limit of quantification (LOQ) values were available. For dioxins + dl-PCBS, lower bound (LB) and upper bound (UB) values were available for several samples per fish species. In this study,

conservative estimates for the contaminants were used: total mercury was regarded as methyl mercury, and for dioxins + dl-PCBs, the UB values were used for each sample. It is generally found that about 80% - 100% of total mercury in fish is methyl mercury (18), and UBs most likely represent an overestimate of the true values (6). For mercury samples with low concentrations, and hence no data values, the mean of LOD and LOQ were used. The means of the sample concentrations were used as mean contaminant concentrations in this study.

For some species of fish, intake data on subcategories were available. For example, intake data for both raw and smoked salmon were available. In those cases, the weighted arithmetic mean, with mean observed intake for the different categories serving as weights, was calculated as mean concentration for the species. For the subgroups lean and fatty fish, mean nutrient and contaminant concentrations were also calculated as weighted arithmetic means, for women and men. For the subgroup 'other lean' fish, concentration data for scrub, representing 86% of that group, was used. Similarity, for 'other fatty' fish, concentration data for trout, representing 87% of that group, was used. See the mean concentrations used in this study in **Table 2**.

Nutrition-based recommendations. Recommended daily intakes for EPA + DHA (19) and vitamin D (20) are shown in **Table 3** and converted to weekly values. For vitamin D, there is an upper level of 100 µg/day (21). In this study, this upper level was neglected after establishing that the contaminant constraints were limiting the fish intake amount long before.

Contamination-based tolerable intakes. Tolerable weekly intakes per body weight of methyl mercury (18) and dioxins + dl-PCBs (22) are shown in Table 3. The per-body-weight values were converted to individual values by multiplication with the self-reported body weights, or with mean body weight when no body weight was reported.

177 **Background exposures.** Since other sources than fish may provide nutrients and contaminants, the
178 recommended daily intakes and tolerable weekly intakes were multiplied by the scaling factor: '100 -
179 background exposure (%)'. The background exposure is not easily quantified because it is dependent
180 on the whole individual diet and on potential environmental exposure. Therefore, the impact of
181 background exposure was analyzed by scenario analysis.

182 A baseline scenario was defined, indicating the most likely background exposure. The background
183 exposures of EPA + DHA, methyl mercury, and dioxins + dl-PCBs were used from a French study (5).
184 For vitamin D, the value 39% was not considered representative for Denmark, and it gave no feasible
185 solutions. Therefore, a higher background exposure was used. The mean intake of vitamin D in
186 Denmark is 4.8 µg/day (23), and this intake is considered to provide sufficiently high levels of vitamin
187 D in the population. Fish is assumed to contribute 50% of the vitamin D intake in Denmark (24), and
188 therefore it was assumed that Danes acquire 2.4 µg/day from other sources than fish. Hence, the limit
189 value in the baseline was set as 2.4 µg/day. This corresponds to 76% background exposure with a
190 recommended intake of 10 µg/day.

191 Furthermore, to study the importance of the assumptions on the background exposures, eight
192 alternative background exposure scenarios were defined and studied, by visual comparison of feasible
193 region for different scenarios. The scaling factor values for background exposures for the baseline and
194 the alternatives are given in **Table 4**. For vitamin D, three alternatives were chosen because the
195 background exposure of vitamin D is partly dependent on the contribution from sunlight, and therefore
196 highly uncertain. EPA and DHA are well known to come mainly from fish, and therefore only one
197 alternative was chosen. The background exposure from dioxins and dl-PCBs is more uncertain, and
198 hence two alternatives were chosen. Fish is known to be the one significant source of methyl mercury,
199 hence only the baseline was considered.

200 **Software**

201 The models were implemented in Matlab R2015b (version 8.6). To solve the problems CVX was used,
 202 a package for specifying and solving convex programs (25). The statistical analyses were also
 203 performed in Matlab R2015b (version 8.6).

204 **Statistical analysis**

205 The Lilliefors test for normality was run for observed and modeled fish intakes. The equality between
 206 the medians of the modeled and observed intakes was tested using Wilcoxon matched-pairs signed-
 207 rank test. All tests were run with a significance level of $\alpha = 5\%$.

208 **Results**

209 This section is divided between the 2D and 8D models. The modeled intakes represent a proposed
 210 fish intake for each individual in the study population. The baseline scenario (Table 4) is the
 211 background exposure used for all modeled intakes.

212 **2D models: subgroups lean and fatty fish (d=2)**

213 **Feasible regions.** The feasible regions with baseline background exposure for the average-weight
 214 woman (69.7 kg) and average-weight man (84.4 kg) (**Figure 2**) are created by the lower nutrient
 215 constraints and the upper contaminant constraints. The recommended fish intake in Denmark meets
 216 all constraints of the model for both women and men. For men, the feasible region is larger than for
 217 women because the upper contaminant constraints are body weight dependent. The feasible regions
 218 for the eight alternative background exposure scenarios (Table 3) for the average-weight woman
 219 (**Figure 3**) show the variation due to background exposure (the variation is similar for women and
 220 men). The feasible region for scenario D is identical with the baseline feasible region (Figure 2a) since
 221 the vitamin D constraint is the lower limit and a lower background exposure of EPA + DHA does not
 222 affect the region. Recommended fish intake in Denmark lies within the feasible region for scenarios B

223 through G. Typically, scenarios A and H have a lower background exposure to vitamin D. The
224 increased demand for vitamin D requires a high intake of fish that may lead to exceeding the tolerable
225 weekly intake of dioxins + dl-PCBs.

226 **Modeled intakes.** With the 2D QP model, all 3,016 individuals had feasible solutions. The mean (with
227 standard deviation) suggested an increase in fish intake (delta intake) for women of 25(30) g of lean
228 fish/wk and 80(90) g of fatty fish/wk; and for men these numbers were 21(41) g/wk and 73(116) g/wk,
229 respectively (**Figure 4, Supplemental Table 1**). The vitamin D constraint often determines the
230 proposed increase in fish intake for those who presently consume too little fish. This results in a line of
231 points in figures, as the lower vitamin D constraint is not body weight dependent. Some consumers
232 with a high intake of fish are proposed to reduce their fish consumption due to the upper constraints of
233 the contaminants. This does not occur as a line of points as it occurs less frequently and the individual
234 constraints differ due to the variation in body weight.

235 With the 2D QPr model, an optimized intake was found for 1,397 women and 1,279 men. Hence, there
236 was no combination of the reported intake of lean and fatty fish meeting all constraints for 340
237 individuals. These individuals need to expand their fish intake repertoire to get feasible solutions. The
238 results are available in **Supplemental Table 2**.

239 The cumulative distributions for the difference between modeled and observed intake (delta intake)
240 with the 2D QP and QPr models for women are shown in **Figure 5**. For men, the figures are similar,
241 hence they are not shown. For example, looking at the QP model, 20% of the women should increase
242 their lean fish intake with more than 53 g/wk (this number is found by reading the delta intake
243 corresponding to the y-value 0.8 for the lean fish curve). Both the QP and QPr models suggest a
244 larger change in intake of fatty fish than lean. For the QPr model, note that there is a sharp edge in the
245 lean fish curve for individuals proposed to increase their intake with more than 50 g of lean fish/wk.
246 These individuals receive a zero delta intake of fatty fish from the models, so they are suggested to

increase their lean fish intake more. Also, note that the maximum delta intake of lean fish for the QPr model is 615 g/wk, as compared with 179 g/wk for the QP model. As shown in the feasible region for the average weight woman (Figure 2a), the minimum feasible intake of lean fish, when not consuming fatty fish, is 622 g/wk. Hence, a woman who did not report any fatty fish intake is suggested to increase her lean fish intake with 615 g/wk, while her reported intake was 7 g/wk of lean fish.

8D models: eight species of fish (d=8)

Modeled intakes. With the 8D QP model, all 3,016 individuals had feasible solutions. The mean (with standard deviation) suggested an increase in fish intake (delta intake) for women of 14(24) g of lean fish/wk and 63(75) g of fatty fish/wk; and for men these numbers were 12(35) g/wk and 55(103) g/wk respectively (**Supplemental Table 3**). The 3,016 modeled intakes of the 8D QP model are plotted in two-dimensions by summing the species of lean and fatty fish respectively (as compared with the 2D models where lean and fatty fish were the optimization variables), see **Figure 6**. Lower intakes do not create as clear a line as for the 2D models (Figure 4): a result of the eight-dimensionality that implies higher flexibility.

With the 8D QPr model, only allowing reported species in the modeled intake, an optimized intake was found for 1,262 women and 1,124 men. The results are given in **Supplemental Table 4**.

The cumulative distributions for delta intake for the 8D QP model are shown in **Figure 7**. As the cumulative distributions look similar for women and men, only those for women are shown. For fatty fish species, the model suggests the largest change in intake for the category 'other fatty', which represents trout. For lean fish species, cod is suggested to be increased the most.

Discussion

268 This study shows how mathematical optimization, specifically quadratic programming, can be used to
269 derive individual food intake that ensure a healthy and safe consumption pattern. This is illustrated for
270 fish, using fish consumption data of 3,016 Danes. For each individual, a proposed fish intake that
271 differs the least from her/his current intake, while meeting several criteria on nutrients and
272 contaminants was modeled. The eight most consumed fish species in Denmark were considered.
273 Allowing non-reported species in the modeled intake, an optimized intake was found for all 3,016
274 individuals. When only reported species were allowed, an optimized intake was found for 2,386
275 individuals (79%). Furthermore, several scenarios for background exposure of nutrients and
276 contaminants were compared for a 2D model (where the subgroups lean and fatty fish were
277 optimized) by showing feasible regions for eight background exposure scenarios as alternatives to the
278 baseline that included the most likely background exposures.

279 Our results show that to follow the current Danish official dietary guidelines regarding intake of fish,
280 most Danes should increase their fish intake, and a smaller fraction should either eat less fish or not
281 change their fish intake at all. We show that when the requirement is to meet the recommendations for
282 EPA + DHA and vitamin D without violating tolerable intake recommendations for methyl mercury and
283 dioxins + dl-PCBs, an intake of 350 g fish/wk of which 200 g should be fatty fish (recommendation in
284 the Danish official dietary guidelines), is not necessary. According to the criteria used in this study,
285 eating this amount is healthy and not harmful, but it requires larger behavior changes than necessary,
286 which may lead to lack of compliance.

287 In general, our results suggest that women need to increase their fish intake more than men, and fatty
288 fish should be prioritized over lean fish for both genders. Within the subgroups, cod and 'other fatty',
289 which is mainly trout, are the species proposed to be increased the most, whereas plaice and
290 mackerel are the species suggested to be increased the least.

291 In general, mathematical optimization methods are suitable for addressing the complexity of data on
292 food intake and dietary requirements, thanks to their ability to deal with several factors simultaneously.
293 The models presented in this paper can be expanded to address additional and/or other nutrients,
294 contaminants, foods, or food (sub)groups. Whole diets can also be optimized (11,13,14). Furthermore,
295 mathematical optimization methods can be expanded to include other food related issues, such as
296 sustainability and economy (26–30).

297 In previous studies on diet optimization, the L_1 -norm was typically used as an objective function, and
298 the optimization problems were transformed into a linear problem (11–14) to ensure unique global
299 minima (12). In this study, quadratic programming with an objective function using the L_2 -norm was
300 preferred for two reasons. First, quadratic programming punishes large deviations and typically makes
301 small changes to almost all elements of the optimization variable. Linear programming, on the other
302 hand, typically makes large changes in a limited number of elements and leaves the others
303 unchanged. Since we are dealing with a change in behavior, our argument is that many smaller
304 changes, as obtained from quadratic programming, are more realistic and achievable than fewer
305 larger changes. The researchers that developed the Dutch food-based dietary guidelines (31) have
306 compared the linear and quadratic programming and their conclusion was that the later gave more
307 achievable results. This was also concluded in the WWF report 'Eating for 2 degrees' (32–34).
308 Second, our method guarantees a unique global minimum without transformation and therefore, as
309 compared to using the L_1 -norm, enables direct interpretation of the constraints (12).

310 In previous diet optimizations, the objective functions were typically standardized across foods by
311 dividing with observed intake of the specific food items (5,11,13,14). This was considered not
312 necessary in this study, as only the consumption of fish was modeled.

313 At present, lack of appropriate data and uncertainty on the recommended and tolerable intakes as well
314 as the background exposures are important limiting factors for intake optimization. Recommended

315 daily intakes and tolerable weekly intakes are based on available scientific evidence, but may change
316 if new data become available. Furthermore, these limits are average values, and thus do not take into
317 account variability in the population, e.g., in terms of food consumption, age, gender or weight (only
318 nutrient limits). As this inter-individual variation is unknown, it cannot be included in our model. If these
319 data were available, our approach could be individualized further to propose more precise individual
320 results. For example, common genetic variations in genes have been shown to determine vitamin D
321 status in Danes (35), and incorporation of such individual information would reduce the uncertainty of
322 the results.

323 Nutrients and contaminant concentrations for fish may vary depending on region of capture, season,
324 whether the fish is farmed or wild, etc. (6). Average values, as used in this study, allow a realistic
325 estimate of long-term consumption and exposure. Furthermore, if data on individual selection of, e.g.,
326 wild/farmed fish and region of capture, were available, the approach could be individualized further.
327 Finally, the intake data (7-day estimated records) are also uncertain due to memory bias of the
328 participants, limited time of reporting, and a potential selection bias of participants.

329 To our knowledge, this is the first intake optimization paper showing the variation in feasible regions
330 due to uncertainty in background exposure. The feasible regions are sensitive to this uncertainty. The
331 vitamin D background exposure appears to be especially important, and also the one most difficult to
332 establish because vitamin D can be obtained from many food products and is thus highly dependent
333 on individuals' diet and sun exposure. For this reason, vitamin D is commonly excluded in intake
334 optimization studies. When a substantial amount of vitamin D is required to come from fish, there is a
335 conflict between vitamin D and contaminants (5,11). In a French fish optimization study (5), the
336 authors removed the vitamin D constraint, and instead maximized the Vitamin D intake. In a French
337 whole diet optimization study (11), the vitamin D constraint was removed, and with the argument that
338 vitamin D can be provided by supplements and sunlight, ignored it in the model. In our study, the

vitamin D constraint was not removed. Our argument was that fish is an important source of vitamin D, and people in Scandinavian countries rely more on vitamin D intake from food, especially in winter. Also, we chose to include vitamin D because our analysis shows that it is an important constraint that cannot be ignored. However, we had to accept a lower limit value in the baseline scenario to obtain feasible results, and therefore considered it to be sufficient that each individual at least reach the mean vitamin D intake from fish in the Danish population.

Options to deal with individual background exposure from food in future research are [1] a whole diet optimization approach (11,13,14) and [2] inclusion of individual intake data of the nutrients and contaminants to calculate individual background exposure from foods other than fish. In both cases, environmental or other specific, individual background exposures still require consideration. The first option would be more data demanding and is less focused on optimizing fish intake, but it would give dietary advice that was more complete. Also, substitution with other foods is a relevant issue, as, when fish intake is increased, the intake of other food(s) is probably decreased. In this paper, no substitution was accounted for. For whole diet optimization, the substitution is dealt with naturally. However, for optimization of a single food item such as fish, a future challenge for diet modeling is to include substitution. With data on individual preferences of substituting foods, the models could be individualized further, and hence give more precise individual recommendations.

Conclusions

It was shown that mathematical optimization, specifically quadratic programming, can be used to derive recommended individual fish intake based on current fish consumption and body weight, that ensure a safe and healthy fish consumption pattern. The model can be extended to other nutrients, contaminants and foods, and utilized to provide recommendations that are adapted to individuals. By minimizing the need for large and eventually unrealistic behavior changes, our hypothesis is that this

approach may have the potential to increase compliance with guidelines. A further development and expansion of this approach may therefore have an impact on the promotion of health and prevention of disease in populations.

Acknowledgments

The authors thank Jens Hinge Andersen for making the contaminant data used in this study available through the EFSA Circle of Trust initiative. The National Food Institute at the Technical University of Denmark thanks the following European governmental organizations participating to the Circle of Trust pilot initiative for sharing the data: Austrian Agency for Health and Food Safety (AGES), Croatian Food Agency, DGAL French Ministry of Agriculture Food and Forestry (France), DGCCRF Directorate General for Competition Consumer Affairs and Fraud Control (France), Finnish Food Safety Authority Evira, Food Safety authority of Ireland, Food Safety Service (SECUALIM) (France), French agency for food, environmental and occupational health safety (Anses, France), Hellenic Food Authority, Ministero della Salute (Italy), National Food Agency (Sweden), National Food Chain Safety Office (Hungary), Netherlands Food and Consumer Product Safety Authority (NVWA), Organisme pour la sécurité et la qualité de la chaîne alimentaire (OSQCA) (Luxembourg), RIKILT - Institute of Food Safety (Netherlands), Risk Assessment Centre (RAC) within the Bulgarian Food Safety Agency, RIVM - National Institute for Public Health and the Environment (Netherlands), State General Laboratory (SGL) (Cyprus), and Veterinary and Food Board of Estonia.

The authors' responsibilities were as follows - M. Pe. and M. J. N. designed research; M. Pe. conducted research and analyzed data; and M. Pe. and M. J. N. wrote the paper. F. S. provided essential material; and S. M. P., M. Po., and F. V. provided essential input during the research and writing the paper. M. Pe. and M. J. N. had primary responsibility for final content. All authors read and approved the final manuscript.

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Table 1: Observed fish intakes from 3,016 participants (1,552 women and 1,464 men) aged 18-75 from the DANSDA study¹

	Women			Men		
	Means±SDs, g/wk	Medians(IQRs), g/wk	nr	Means±SDs, g/wk	Medians(IQRs), g/wk	nr
Total	200±193	149(241)	1,408	245±258	181(318)	1,297
Lean fish (≤5% fat)	92±118	50(138)	1,158	111±155	53(174)	1,065
Cod	37±72	0(46)	703	40±81	0(46)	609
Plaice	25±66	0(9.7)	408	34±101	0(9.7)	387
Tuna	21±49	0(15)	753	25±64	0(19)	698
Other lean	8.9±28	0(0)	246	13±41	0(0)	261
Fatty fish (>5% fat)	108±138	58(161)	1,231	134±191	50(197)	1,089
Salmon	41±68	8.6(54)	924	42±77	0(45)	728
Herring	31±63	1.4(38)	860	49±103	0.72(54)	783
Mackerel	23±40	9.2(33)	947	31±57	9.2(37)	832
Other	12±25	0(8.0)	697	13±31	0(4.4)	551

¹ n =3,016. The observed fish intakes are not normally distributed, according to the Lilliefors test at significance level 5%. DANSDA, Danish national survey of diet and physical activity; nr, number of individuals with reported intake.

Table 2: Nutrient and contaminant concentrations for fish used in this study¹

	EPA+DHA, mg/g	Vitamin D, µg/g	Methyl mercury, µg/g	Dioxins dl-PCBs, pg TEQ/g
Lean fish (≤5% fat)				
Cod	3.1	0.043	0.091±0.085	0.27±0.48
Plaice	6.0	0.011	0.061±0.071	0.75±0.96
Tuna	2.0	0.027	0.22±0.27	1.2±4.0
Other lean	4.2	0.0080	0.082±0.055	0.69
Fatty fish (>5% fat)				
Salmon	16	0.079	0.034±0.034	1.1±2.2
Herring	18	0.095	0.029±0.024	1.4±0.89
Mackerel	26	0.044	0.081±0.11	2.6±1.9
Other fatty	14	0.16	0.034±0.034	1.1±2.2

¹ Values are means ± SDs or only means (when SDs were not available). DHA, docosahexaenoic acid; dl-PCBs, dioxin-like polychlorinated biphenyls; EPA, eicosapentaenoic acid.

Table 3: Recommendations on nutrients and contaminants used in this study¹

	Value	Reference
Recommended daily intake		
EPA+DHA, mg/day	250	(19)
Vitamin D, µg/day	10	(20)
Tolerable weekly intake		
Methyl mercury, µg/kg BW/wk	1.3	(18)
Dioxins + dl-PCB, pg TEQ/kg BW/wk	14	(22)

¹ DHA, docosahexaenoic acid; dl-PCBs, dioxin-like polychlorinated biphenyls; EPA, eicosapentaenoic acid.

Table 4: Background exposure scenarios for visual comparison of feasible regions for average weight Danish woman ^{1, 2}

	Baseline, %	A, %	B, %	C, %	D, %	E, %	F, %	G, %	H, %
EPA+DHA	13	-	-	-	0	-	-	0	-
Vitamin D	76	39	70	95	-	-	-	95	39
Methyl mercury	0	-	-	-	-	-	-	-	-
Dioxins+dl-PCBs	34	-	-	-	-	50	20	-	20

¹ Values are percentage values of total exposure. The background exposure is defined as the exposure from other sources than fish. Baseline background exposure scenario and eight alternative background exposure scenarios, A through H, are shown. Cell marked '-' refers to corresponding baseline value.

² The baseline background exposure scenario was used in the models for generating fish intake levels for all individuals.

Figure legends

Figure 1 Observed fish intakes from 3,016 participants; 1,552 women (A) and 1,464 men (B), aged 18-75 from the DANSDA study. DANSDA, Danish national survey of diet and physical activity.

Figure 2 Feasible region for 69.7 kg Danish woman (A) and 84.4 kg Danish man (B) modelled with two-dimensional QP model. The baseline background exposure is used. The feasible regions are created by the lower constraint on vitamin D, and the upper constraints on methyl mercury and dioxins + dl-PCBs. The lower EPA + DHA constraint does not affect the regions. DHA, docosahexaenoic acid; dl-PCBs, dioxin-like polychlorinated biphenyls; EPA, eicosapentaenoic acid; QP, quadratic programming model allowing all species of fish in modeled intake.

Figure 3 Alternative feasible regions for 69.7 kg Danish woman (A-H) modeled with two-dimensional QP model. The alternative background exposures are used. Scenario A has no feasible solutions. QP, quadratic programming model allowing all species of fish in modeled intake.

Figure 4 Modeled fish intake for 1,552 Danish women (A) and 1,464 Danish men (B) generated with two-dimensional QP model. The figures illustrate how individuals with an observed intake within her/his feasible region get a modeled intake identical with the observed, whereas individuals with an observed intake outside her/his feasible region get a modeled intake on the region border; the point on the feasible region closest to the observed intake. The modeled intakes were significantly different from observed intakes, $P < 0.05$, according to the Wilcoxon matched-pairs signed-rank test. QP, quadratic programming model allowing all species of fish in modeled intake.

Figure 5 Cumulative distributions for delta fish intake (modeled minus observed intake) for 1,552 Danish women modeled with two-dimensional QP model (A) and QPr model (B). The figures give information on how many individuals that are recommended to change their fish intake and how. The fraction of individuals that are suggested to not change (delta intake = 0), decrease (delta intake < 0),

or increase ($\Delta \text{intake} > 0$) their intake can be read from the graphs. QP, quadratic programming model allowing all species of fish in modeled intake; QPr, quadratic programming model only allowing reported fish in modeled intake.

Figure 6 Modeled fish intake for 1,552 Danish women (A) and 1,464 Danish men (B) generated with eight-dimensional QP model. The figures illustrate how individuals with an observed intake within her/his feasible region get a modeled intake identical with the observed, whereas individuals with an observed intake outside her/his feasible region get a modeled intake on the region border; the point on the feasible region closest to the observed intake. The modeled intakes were significantly different from observed intakes, $P < 0.05$, according to the Wilcoxon matched-pairs signed-rank test. QP, quadratic programming model allowing all species of fish in modeled intake.

Figure 7 Cumulative distributions for delta fish intake (modeled minus observed intake) for 1,552 Danish women modeled with eight-dimensional QP model. The figures give information on how many individuals that are recommended to change their fish intake and how. The fraction of individuals that are suggested to not change ($\Delta \text{intake} = 0$), decrease ($\Delta \text{intake} < 0$), or increase ($\Delta \text{intake} > 0$) their intake can be read from the graphs. QP, quadratic programming model allowing all species of fish in modeled intake.